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26th Euroconference on Apoptosis
Cell death in disease: from small molecules to translational medicine

CONFERENCE PROGRAM & ABSTRACT BOOK

October 10-12, 2018
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European Cell Death Organization
ECDO

26th Conference of the European Cell Death Organization

CELL DEATH IN DISEASE: FROM SMALL MOLECULES TO TRANSLATIONAL MEDICINE

October 10–12, 2018 – Saint Petersburg, Russia

CHAIR PERSONS

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INVITED SPEAKERS

Patrizia Agostinis, University of Leuven, Belgium
Marcus Conrad, Helmholtz Zentrum München, Germany
Klaus-Michael Debatin, Ulm University, Germany
Vishva Dixit, Genentech, USA – CDD Jürg Tschopp Prize Lecture
Ana Garcia-Saez, University of Tübingen, Germany
Carmen Garrido, INSERM, France
Eyal Gottlieb, Technion-Israel Institute of Technology, Israel
Andrei V. Gudkov, Roswell Park Cancer Institute, Buffalo, USA
Thanos Halazonetis, Geneva University, Switzerland
Bertrand Joseph, Karolinska Institutet, Sweden
Anthony Letai, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA
Marion MacFarlane, MRC Toxicology Unit, UK
Tak W. Mak, Princess Margaret Cancer Centre, Canada
Shigekatzu Nagata, Osaka University, Japan
Sergei Nedospasov, Engelhardt Institute of Molecular Biology, Russia
Mauro Piacentini, University of Roma, Italy
Andreas Strasser, Walter and Eliza Hall Institute of Medical Research
Henning Walczak, University College London, UK
Xiaodong Wang, National Institute of Biological Sciences, China
Tamotsu Yoshimori, Osaka University, Japan

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SELECTIVE SMALL MOLECULE STABILISERS/ACTIVATORS OF P53(Y220C) MUTANT

Regina Sayarova[1], Raniya Nazyrova[1], Rimma Mingaleeva[1], Olga Kartseva[1], Irina Glagoleva[1], Natalya Alexandrova[1], Azzam Hamad[1], Razan Subani[1], Vitaly Chasov[1], Rafil Khairullin[1], Regina Miftakhova[1], Matthias Baud[2], Albert Rizvanov[1], Emil Bulatov[1]

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In about 50% of tumor cases inactivation of p53, a key oncosuppressor and transcription factor, is caused by mutations that primarily affect DNA-binding domain. Oncogenic missense mutation Y220C is the ninth most common for p53 and is annually observed in about 100,000 new diagnosed cancer cases worldwide. Presence of this mutation disturbs tertiary structure of the p53 DNA-binding domain that further leads to destabilization of the whole protein, its partial denaturation and loss of transcriptional activity. Selective small molecule modulators of p53(Y220C) mutant can be used to structurally stabilize the protein and restore its impaired transcriptional functions. Aminobenzothiazole MB725 and its derivatives represent a highly promising scaffold for development of potent stabilisers/activators of p53(Y220C) mutant.

In this study we employ a wide spectrum of modern interdisciplinary methods and approaches to explore how small molecules could effectively restore biological activity of p53(Y220C) mutant. This includes organic synthesis, structural biology and a range of molecular and cell biology techniques. Mutant p53(Y220C) and p53-/- MCF7 cell lines are being generated using CRISPR/Cas9 gene editing technology. Cellular effect of the compounds is investigated using following methods – assessment of cytotoxicity by MTS test; monitoring of cell proliferation and viability using xCELLigence real time cell analysis; analysis of p53-dependent gene expression by quantitative real-time reverse transcription PCR; quantitative analysis of alterations in intracellular protein levels by immunoblotting; cytofluorometric analysis of cell cycle and programmed cell death. Evaluation of mutant p53(Y220C) stabilization against intracellular proteasomal degradation to be performed using fluorescent reporter system. In addition, we studied interaction of MB725 and its analog with recombinantly expressed and chromatographically purified p53 and p53(Y220C). For that we used two biophysical methods – surface plasmon resonance to measure interaction Kd and differential scanning fluorimetry to estimate protein thermal stability in presence of the compounds. The results can be used to develop personalised therapeutics targeting not only Y220C, but also other p53 mutants.

The study was supported by Grant of the President of Russian Federation MK-4253.2018.4 to E.B. and RFBR 18-34-00702 mol_a Grant to R.S.

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THE KNOCKOUT OF P53-SPESIFIC METHYLTRANSFERASE SET7/9 LEADS TO APOPTOSIS INCREASE IN A549 LUNG CANCER CELLS UNDER GENOTOXIC CONDITIONS

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Lysine-specific methyl transferase Set7/9 was first described as a histone H3-specific methyltransferase. Later, Set7/9 was shown to methylate about 30 non-histone proteins, including the p53 tumor suppressor. TP53 is a known regulator of cell cycle, autophagy, and apoptosis involved in cellular response to various forms of stress.

Previous experiments have demonstrated the role of Set7/9 in p53 response and cellular sensitivity to drugs. By means of the CRISPR/Cas9 genome editing system, we created Set7/9 knockout in A549 human non-small lung carcinoma cells. Using this model cell system, we showed that knockout of Set7/9 increased the sensitivity to genotoxic drugs doxorubicin and cisplatin, and induced apoptosis in cells treated with etoposide and doxorubicin.

We also demonstrated that Set7/9 knockout caused a decrease in the formation of gamma H2A.X repair foci. Based on our findings, we assume that Set7/9 methyltransferase is involved in DNA damage response and can be considered as a potential marker for the efficacy of genotoxic chemotherapy against lung cancer.

This work was funded by RSF No 17-75-10198.

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NEW INHIBITORS OF THE BCL-2 FAMILY MEMBERS DERIVED FROM NATURAL DRIMANE SESQUITERPENES

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Proteins of the BCL-2 family play a major role in cellular homeostasis since they regulate apoptotic cell death through dynamic interactions between the anti- and pro-apoptotic members. Over-expression of anti-apoptotic members (BCL-2, BCL-xL, MCL-1...) participates in the development of tumors as well as in their resistance to treatments (chemotherapy, radiotherapy). Synthetic inhibitors targeting these anti-apoptotic proteins have therefore been developed, some of which being currently in clinical trials.

Natural products possess a unique and vast chemical diversity and are therefore playing a significant role in drug discovery and development processes. Since the 1940's, 75% of the 175 small molecules used in cancer therapy are either natural products